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Magnetic Resonance Imaging and Computed Tomography of the Brain—50 Years of Innovation, With a Focus on the Future

Val M. Runge, MD, Shigeki Aoki, MD,† William G. Bradley Jr, MD, PhD,‡ Kee-Hyun Chang, MD,§ Marco Essig, MD,|| Lin Ma, MD, PhD,¶ Jeffrey S. Ross, MD,# and Anton Valavanis, MD***

Abstract: This review focuses specifically on the developments in brain imaging, as opposed to the spine, and specifically conventional, clinical, cross-sectional imaging, looking primarily at advances in magnetic resonance imaging (MRI) and computed tomography (CT). These fields are viewed from a perspective of landmark publications in the last 50 years and subsequently more in depth using sentinel publications from the last 5 years. It is also written from a personal perspective, with the authors having witnessed the evolution of both fields from their initial clinical introduction to their current state. Both CT and MRI have made tremendous advances during this time, regarding not only sensitivity and spatial resolution, but also in terms of the speed of image acquisition. Advances in CT in recent years have focused in part on reduced radiation dose, an important topic for the years to come. Magnetic resonance imaging has seen the development of a plethora of scan techniques, with marked superiority to CT in terms of tissue contrast due to the many parameters that can be assessed, and their intrinsic sensitivity. Future advances in MRI for clinical practice will likely focus both on new acquisition techniques that offer advances in speed and resolution, for example, simultaneous multislice imaging and data sparsity, and on standardization and further automation of image acquisition and analysis. Functional imaging techniques including specifically perfusion and functional magnetic resonance imaging will be further integrated into the workflow to provide pathophysiologic information that influence differential diagnosis, assist treatment decision and planning, and identify and follow treatment-related changes.

Key Words: brain, magnetic resonance imaging, central nervous system, computed tomography, gadolinium, technology

(*Invest Radiol* 2015;00: 00–00)

Studies published in *Investigative Radiology* that have received the highest number of citations (specifically the top 250) include a diverse but critical set of advances for our field. In this section, 10 important central nervous system (CNS) studies are highlighted. The number 4 most cited study quantitates the relaxation properties of the commercially available gadolinium chelates at the clinically relevant field strengths used today, 1.5 and 3 T.[1] This article also serves as the reference standard in the field, although it is likely to be displaced with time by a more recent publication in the journal, which expands the comparison to include 1.5, 3, and 7 T, and specifically compares the agents in the most relevant environment, that of human blood.[2] One focus of the journal historically has been contrast media, and the appearance of an additional study in the top 50 is not surprising. The number 21 on this list is the first demonstration of significant differences in relaxivity between extracellular gadolinium chelates, depending upon their design. This is a potentially important differentiator between agents, with implications in routine clinical use.[3] The 31st most cited study introduces the topic of mean transit time in computed tomography (CT), launching the field of cerebral perfusion for cross-sectional imaging,[4] which is now a widely used clinical measure for both CT and magnetic resonance imaging (MRI). Evaluation of cerebral ischemia and neoplastic disease today incorporates measurement of cerebral blood volume, in the first disease category for prognosis and therapeutic decision making and in the second for differential diagnosis. Also in the top 250 cited articles is the first description of diffusion-weighted imaging (DWI),[5] and its potential as an important additional noninvasive MR marker. The importance of diffusion imaging lies only just behind the fundamental parameters of T1 and T2, and once available was rapidly integrated into clinical routine. Additional critical advances in CT that are highlighted by articles in the top 250 cited studies include the first description of sagittal and coronal reformatted images obtained from axial scanning[6] and the first description of stereotactic head frame use.[7] Both techniques are now routinely used and today represent standard clinical practice. In MRI, additional important advances highlighted by articles include the first demonstration of brain mapping (functional magnetic resonance imaging), which was shown for the visual cortex,[8] the advent, challenges, and advantages of 3 T for brain imaging,[9] and the description of an early important contraindication for MR, the presence of a deep brain stimulator.[10] Another landmark article in the top 250 articles published concerns health policy, specifically the evaluation of research methods/publication by disease, level of impact, and quality of research.[11]

The past 5 years of publications in *Investigative Radiology* were evaluated in greater detail, looking for trends as well as important focus areas. Forty references from this period are highlighted, and they establish the most important areas of CNS research for the next decade, as well as the disease entities of greatest focus (cerebral ischemia and CNS neoplasia). Regarding cerebral ischemia, the focus in the radiologic literature is predominantly on improved imaging technique. Computed tomography has developed to the extent that whole-brain perfusion is now possible, being previously limited to only a few slices.[12] This of itself is a critical advance but just as important is the acquisition of such data with markedly lower radiation dose (Fig. 1). Widespread availability of CT perfusion today makes triage of patients presenting with clinical symptoms of ischemia possible, which is of critical importance relative to therapy. The availability of CT perfusion also has had other benefits, for example, improving detection of smaller ischemic lesions.[13] Automated CT techniques, based on image processing alone or on the characterization of tissue using dual-energy CT, will eventually be a part of mainstream clinical practice, improving lesion detection and characterization. Automatic detection and volume estimation of infarcts, in particular acute infarcts that are quite subtle on CT, is well within the grasp today of computer technology.[14] In another example, the limited ability to differentiate between hemorrhage and calcification within lesions still detracts from the clinical value of CT, with dual energy offering a major advance in this role.[15] Color-coded CT angiography, a new method of displaying dynamic cerebral CT angiography, provides the individual interpreting the exam with important additional diagnostic

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From the *Clinic for Neuroradiology, Institute for Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland; †Department of Radiology, Juntendo University, Tokyo, Japan; ‡Department of Radiology, University of California San Diego Health System, San Diego, CA; §Department of Radiology, Soonchunhyang University Hospital, Bucheon, Republic of Korea; ||Department of Radiology, University of Manitoba, Winnipeg, Manitoba, Canada; ¶Department of Radiology, PLA General Hospital, Beijing, China; #Department of Neuroradiology, Barrow Neurological Institute, Phoenix, AZ; and **Department of Neuroradiology, University Hospital Zurich, Zurich, Switzerland.

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Reprints: Val M. Runge, MD, Clinic for Neuroradiology, Institute for Diagnostic and Interventional Radiology, University Hospital Zurich, Raemistrasse 100, Zurich, Switzerland 8091. E-mail: val.runge@mac.com.

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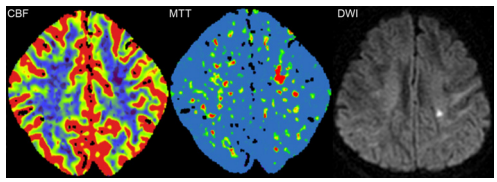

FIGURE 1. Whole-brain CT perfusion, now clinically available due to technologic innovations, improves diagnostic utility and makes possible the detection of small acute brain infarcts. The CT scans in this patient, specifically the cerebral blood flow and mean transit time images, were acquired 1.5 hours after symptom onset and reveal a small ischemic lesion in the left central semiovale. The lesion was confirmed by MRI (DWI), which was performed 2 days later. Reprinted with permission from Thierfelder et al.[13] Figure 1 can be viewed online in color at www.investigativeradiology.com.

information, including specifically differentiation between antegrade and retrograde flow and leptomeningeal collateralization (Fig. 2).[16] Similar color-coding is being applied in MRI, for applications such as the supply and drainage of arteriovenous malformations and for collateral flow in cerebrovascular disease. More fundamental research is being conducted both in animal models and in patients, which will expand our understanding of ischemia[17,18] and lead possibly to innovative therapies.[19] Carotid vessel wall imaging,[20,21] and improved evaluation of flow within the carotid artery,[22] may add as well to our ability to evaluate patients, their risk, and the severity of the disease present.

Research focused on neoplastic disease spans the range from animal models of disease to computer postprocessing techniques for improved diagnosis. Metastatic disease is, within the more general category of neoplasia, a major area of research both due to its clinical importance (and frequency) and its amenability to improved diagnosis. Much can be done with MRI techniques to further improve lesion detectability. The best acquisition techniques are still being identified and refined.[23–25] Computer-aided image evaluation will likely be a mainstay of diagnostic reporting, although currently in its infancy.[26] Computed tomography techniques also continue to evolve, particularly the use of dual energy, with substantial possibilities for improved lesion delineation and image quality, particularly in soft tissue.[27] Treatment monitoring is a further area for which MRI plays a critical role, with more extensive clinical evaluation and definition of the most important parameters needed.[28] A challenging area that remains is the failure of MRI contrast enhancement to detect all metastatic lesions within the brain.[29] Chemistry is far advanced in comparison to 30 years ago when the gadolinium chelates were first developed. Lesion detectability and many other clinically important parameters could markedly benefit if research within industry continues, specifically development of the next generation of intravenous MRI contrast media, with a substantial improvement in relaxivity. Unfortunately, the cost of such development due to regulatory issues has spiraled beyond control, dimming such prospects.[30]

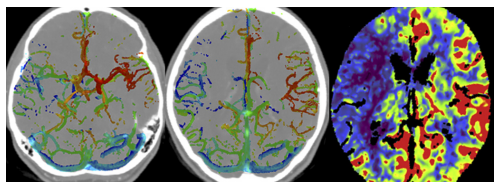

FIGURE 2. Color-coded CT angiography, a recent innovation with applicability in acute infarction, is shown in a patient with an occlusion of the right internal carotid artery. At the 2 levels presented, there is delayed flow within the right middle cerebral artery (MCA) vessels, with collateralization via the anterior communicating artery to the MCA. From the CT perfusion study, cerebral blood flow is markedly reduced as well in the right MCA territory. Reprinted with permission from Thierfelder et al.[16] Figure 2 can be viewed online in color at www.investigativeradiology.com.

Further developments in MRI technique, both acquisition and postprocessing, should have major impact upon utilization of this modality over the next decade. Innovative studies in *Investigative Radiology* illustrate the current advances being made in MR angiography (MRA),[31] quantification of perfusion and permeability,[32] detection and quantification of iron,[33] further image acquisition techniques for improved lesion detectability and quantification,[34] and new functional evaluations, with mainstream application for large clinical subpopulations.[35] The likely focus of MR development in the next decade will be in image reconstruction and postprocessing, rather than new acquisition sequences with different tissue contrast, and specifically involving the field of data sparsity.[36] For conventional imaging, this approach has the potential for a 2-fold to 4-fold increase in scan speed, whereas in dynamic techniques such as MR angiography, the potential is on the order of more than 10-fold.

The field of 7 T is very much in its infancy in terms of routine clinical use in the brain. Future clinical scanners might not be 7 T per se but simply substantially higher in field strength than the premier clinical 3 T MR systems of today. It is also possible that such ultrahigh field scanners might develop a niche for clinical imaging in the high-end private world (with direct fee for service), which has the financial resources to purchase and maintain such systems, and which is also not dependent upon medical insurance plans and reimbursement. Advances are ongoing in brain imaging, with clinical studies based on scanner and sequence acquisition advances demonstrating the potential for brain imaging at an intrinsic resolution and with tissue contrasts not possible at 3 T (Fig. 3).[37–40] As with other specific techniques such as susceptibility weighted imaging,[39] time of flight magnetic resonance angiography at ultrahigh field should be markedly superior to that at 3 T. Advances in TOF imaging technique are ongoing, with amelioration of SAR constraints enabling venous suppression,[41] improving excitation fidelity, leading to higher contrast, and achieving smooth slab transitions.[42] Carotid imaging at 7 T has attracted substantial attention, given the importance of spatial resolution in evaluating the carotid wall and atherosclerotic disease.[43–45] Other specialty areas within the CNS where ultrahigh field MR could easily surpass 3 T in terms of diagnostic efficacy include the orbit,[46] sella, and internal auditory canal. These are all areas where signal-to-noise ratio (SNR), contrast-to-noise ratio, and spatial resolution are critical for diagnosis. Although imaging of other nuclei has yet to have a clinical impact (despite early predictions, which were made even for imaging at 1.5 T), ultrahigh field MR offers greater potential in this area. Early imaging results for sodium in the evaluation of astrocytomas reveal its value for differentiation on the basis of tumor grade, as well as providing additional lesion characterization.[47]

Magnetic resonance-positron emission tomography (PET) resembles in its development the field of MR itself. Its introduction was

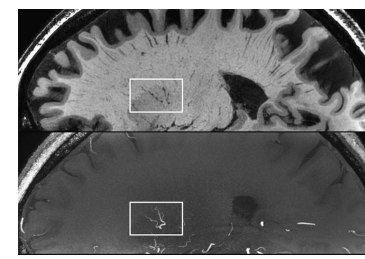

FIGURE 3. Seven tesla offers unparalleled spatial resolution in imaging of the brain, opening new opportunities both for the study of normal anatomy and disease. In the example presented, 7 T offers detailed visualization of the perivascular spaces in the basal ganglia in an elderly woman, which is of potential utility in the study of these fluid-filled cavities in aging and small vessel disease. Note also the prominent generalized dilatation of the perivascular spaces. T1-weighted and 3-dimensional (3D) time of flight magnetic resonance angiography images are presented. Reprinted with permission from Bouvy et al.[37]

marked by very high costs and long exam times, with acceptance limited as well by the existence of a prior well-validated competitor, PET-CT (the competitor for MR upon its introduction was CT itself). MR-PET offers many advantages, such as true simultaneity of acquisition, the possibility of diffusion tensor imaging,[48] and metabolic mapping with spectroscopy.[49] Validation studies with the first commercial units show excellent quantification and stability,[50] with more than 50 units in place worldwide as of 2015.

Substantial advances have also occurred in CT brain imaging in the last 5 years, with the latest scanner and software design providing multiple mechanisms to lower radiation dose.[51] Of importance for brain is the use of lower kV (≤80), offering both lower radiation dose and higher sensitivity to iodinated contrast media. This is particularly important for CT angiography.[52,53]

Not to be overlooked in this assessment, however, is the marked improvement in image quality and imaging technology over the past decades (Fig. 4). This is for all modalities, including MR, CT, and digital subtraction angiography. For example, the latter (flat panel CT) can now provide excellent cross-sectional images, with soft tissue contrast approaching that of dedicated CT units. Overall image quality has advanced to a remarkable extent, in particular for MR, with scan times decreasing by factors of 10 to 100 since the early 1980s. In regard to intravenous contrast media for CT (and digital subtraction angiography), the nonionic iodinated contrast media have now replaced their ionic counterparts. In addition, 1988 marked the clinical launch of the gadolinium chelates for MR as intravenous contrast media. In the latter field, there has been a recent trend toward use only of the macrocyclic agents because of their superior safety profile. The gadolinium chelates are critical to diagnostic MRI of the CNS, with more than 300 million total administrations to date worldwide, and approximately 30 million

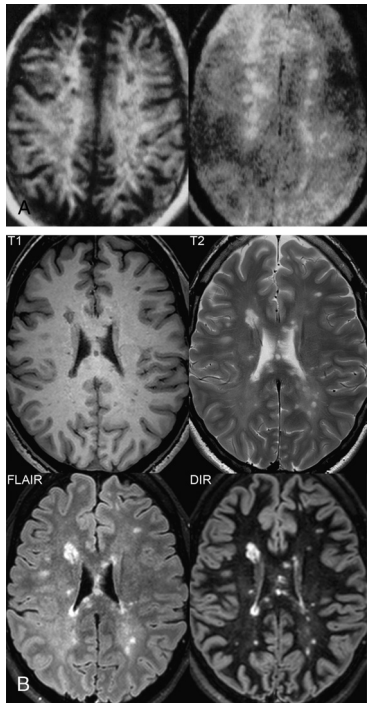

FIGURE 4. State of the art in 1984, a patient with multiple sclerosis (A). The images were acquired at 0.5 T, with a voxel size of $10 \times 2.2 \times 2.2$ mm^3. Both images were acquired using 3D spin echo technique, with scan times respectively of 47 and 37 minutes. The left-hand image is T1-weighted, an inversion recovery technique, and the right-hand image is T2-weighted, however, with repetition time = 1000 milliseconds. This is compared to state-of-the-art images in 2015 (B), also in a patient with multiple sclerosis, imaged at 3 T. DIR indicates double inversion recovery. In-plane resolution was submillimeter, with slice thicknesses of 1 to 4 mm dependent upon technique and scan times on the order of 5 minutes or less for each imaging sequence. Reprinted with permission from Runge et al (*AJR Am J Roentgenol.* 1984;143:1015–1026) and Runge et al (*Neuroradiology: The Essentials with MR and CT*. New York, NY: Thieme Medical Publishers; 2015).

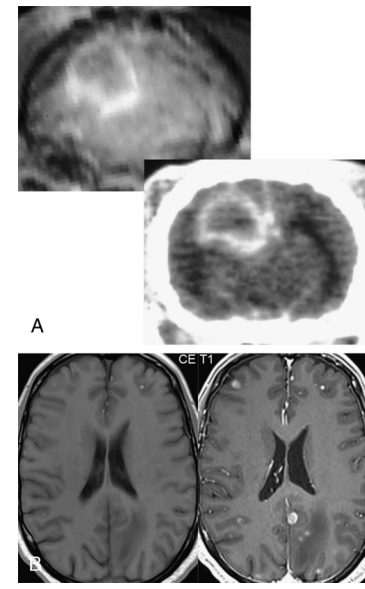

FIGURE 5. The efficacy of a gadolinium chelate for improving lesion detection and differential diagnosis in the brain was first shown in 1984, using a dog brain abscess model. This work received the Dyke award that year from the American Society of Neuroradiology. A coronal postcontrast T1-weighted image at 0.5 T is presented from that research (A), together with the matching enhanced coronal CT, both depicting a large ring-enhancing lesion. Today, intravenous contrast administration is broadly applied for brain imaging in MR with widespread utility. Images obtained at 3 T in a patient with metastatic melanoma are presented, both precontrast and postcontrast. Although several small lesions are visualized in the frontal lobes, precontrast (likely due to hemorrhage), the devastating extent of disease in this patient is only evident postcontrast. Reprinted with permission from Runge et al (*AJNR Am J Neuroradiol.* 1985;6:139–147) and Runge et al (*Neuroradiology: The Essentials with MR and CT*. New York, NY: Thieme Medical Publishers; 2015).

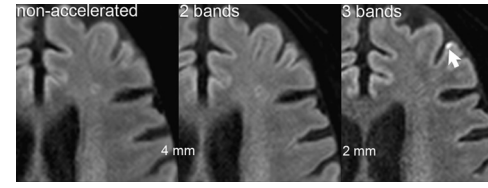

FIGURE 6. MRI at 3 T of a small cortical acute infarct (arrow) illustrating simultaneous multislice accelerated diffusion-weighted echo planar imaging. The advent of this technique is analogous to that of multislice 2-dimensional imaging in the 1980s, and as such may represent one of the major image acquisition innovations in the current decade with widespread clinical applicability. Using an acceleration factor of 3 in combination with a reduction in slice thickness, 2-mm sections through the entire brain can be acquired in a reasonable scan time, with image quality (and SNR) comparable to the 4-mm standard diffusion-weighted EPI acquisition. Because of the thicker section (4 mm), this small cortical infarct was not seen on the conventional readout segmented DWI acquisition (readout segmentation of long echo-trains) or on the accelerated 2-band scan but was noted on one of the two 2-mm sections acquired at this level, an advance made possible by the use of slice acceleration and in this instance 3 bands.

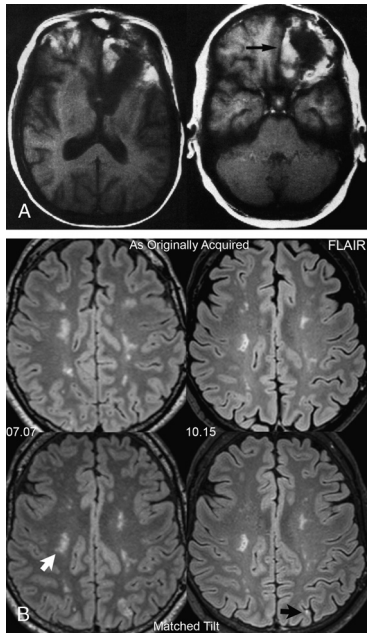

FIGURE 7. Then and now, standardization of image tilt. As early as 1987, inconsistent head positioning was recognized as a problem in clinical imaging, with suggestion of standardization using a tilt in the axial plane. In the example presented (A), improved depiction of enhancing tumor (arrow) is noted in the low left frontal lobe with this approach. Standardization of imaging plane is an important key today to good clinical practice (B), with automatic image alignment (if implemented by the technologist) as a standard part of prescan adjustments. Watershed infarcts are presented on FLAIR images from an examination the week after clinical presentation (left column) and at 3 months (right column). Images in the upper row are the original axial reformatted images from the 3D data sets; the images in the lower row are reformatted to match imaging plane for the 2 examinations. Note that by standardization of the displayed imaging plane, the larger deep white matter infarct on the right (white arrow) can now be easily identified on the follow-up examination, and its evolution assessed, with gliosis replacing the previously identified edema, in a slightly smaller area of involvement, with central cavitation. Comparison of a cortical lesion in the superior parietal gyrus on the left (black arrow), now enabled by the standardization of the presented axial plane, reveals extensive resolution of edema with only a pinpoint area of gliosis remaining. Reprinted with permission from Runge et al (*Magn Reson Imaging*. 1987;5:421–430) and Runge (*Imaging of Cerebrovascular Disease*. New York, NY: Thieme Medical Publishers [in preparation]).

enhanced MR procedures per year. Half of these are for CNS imaging, where the gadolinium chelates play a critical role for both disease detection and differential diagnosis (Fig. 5). Evaluation of tissue perfusion, and contrast-enhanced MRA, would also not be possible without this class of contrast media. Research into development of a new generation of contrast media is ongoing for both CT and MR, with the reader referred to the specific article in this issue of *Investigative Radiology* focusing on intravenous contrast media.

Two software developments in MRI, slice acceleration and sparse sampling, which will see continued attention over the next decade, deserve discussion because of their potential impact long term. For slice acceleration techniques (simultaneous multislice or multiband imaging), the work to date is most advanced involving echo planar DWI.[54–58] Multiple slices are acquired simultaneously using blipped controlled aliasing in parallel imaging results in higher acceleration technique with individual slices then reconstructed using a slice generalized autocalibrating partially parallel acquisition method. An additional requirement is a phased array coil with sufficient elements in the slice encoding direction (and thus appropriate coil designs with high coil density). This approach offers a substantial decrease in image acquisition time. Alternatively, speed can be traded for increased spatial resolution, or with DWI increasing the number of diffusion directions sampled. With the current implementation, in conventional 2-dimensional brain imaging, slice acceleration factors of 2 or 3 can be used, preserving SNR when compared with the identical nonaccelerated scan, with little to no image artifacts (Fig. 6).[59] The second technique, sparse sampling, has also been referred to in the literature by the terms *highly undersampled*, *highly accelerated*, and *compressed sensing*. Development of this technique is likely to take longer than that for slice acceleration because of rapid ongoing evolution of the approach and the need for fast image reconstruction. Sparse sampling is possible and would in theory be of great value, permitting faster or higher resolution imaging, in many instances in current clinical magnetic resonance applications. This is due to the redundancy of data that is currently sampled, with image reconstruction theoretically possible using only a small subset of this data, without a loss in diagnostic quality. Applications in CNS MR that might benefit the most, and thus be implemented earliest, include perfusion and vessel flow. Time-of-flight, phase contrast, and time resolved contrast-enhanced MRA all can benefit from sparse sampling, with initial publications primarily showing results in volunteer studies.[60–62]

There is also a need in the future to look critically at the implementation in clinical imaging of the available sequences, both to assure the choice of imaging technique that is most sensitive and to standardize quality and time efficiency for maximum throughput (Fig. 7). The latter is a continuing mandate by the medical insurance system and the governments of the G7. An example of the former is the need for better dissemination of knowledge concerning the most sensitive scans techniques for disease detection, with a primary example being screening and follow-up examinations for intracranial metastatic disease.[24]

One important remaining topic is that of diffusion tensor imaging (and next-generation diffusion MR), with future development benefiting from many of the innovations and advances previously described. The signal in DWIs is mainly determined by the microstructure of a cell and its organelles (on the scale of micrometers), in distinction to that of T1- and T2-weighted images, which is mainly determined by molecular structures (on the scale of nanometers). Precise analyses of diffusion MR provide intracellular and extracellular fraction changes of water (conventional DWI), axonal/myelin-sheath direction and deterioration (diffusion tensor imaging),[63–65] and other microstructural information such as axonal diameter (Q-space imaging and other next-generation diffusion metrics). Diffusion MRI is used in quantitative analyses,[64,66] as well as structural connectivity analyses of the brain (Fig. 8) and the spinal cord.[67]

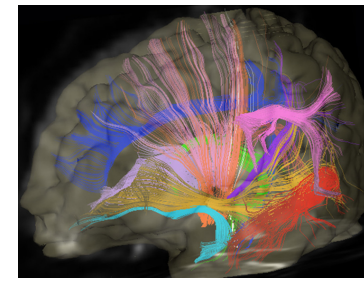

FIGURE 8. Major white matter tracts depicted by diffusion tensor tractography. Blue indicates cingulate fasciculus; light blue, uncinate fasciculus; orange, corona radiata; green, fornix. Figure 8 can be viewed online in color at www.investigativeradiology.com.

In summary, advances in technology have speeded the evolution of both CT and MR as clinical modalities, a process made possible in part by the concurrent evolution of computers, enabling control of the scanners, data handling, and image reconstruction as we know it today. Much of the innovation was driven by the growing importance in clinical medicine of cross-sectional imaging for disease diagnosis and treatment evaluation. Imaging of the brain today occupies a central role in medical care in regard to any question of CNS involvement or symptoms. This represents a marked change and critical advance from 50 years ago (1965) when diagnosis relied upon plain radiographs, pneumoencephalography, and cerebral (x-ray based) angiography.

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